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Prediction of adverse perinatal outcome by fetal biometry: comparison of customized and population-based standards

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KEYWORDS: customized fetal growth standards; estimated fetal weight; growth restriction; mechanical ventilation; neonatal intensive care unit admission; perinatal morbidity; perinatal mortality

CONTRIBUTION

What are the novel findings of this work?
This study compared eight fetal growth standards for prediction of adverse perinatal outcomes based on ultrasound measurements collected within 4 weeks prior to delivery in African-American women. Substantial variability in relative risk and sensitivity for adverse perinatal outcome amongst standards was explained mostly by differences in false-positive rates, yet areas under the receiver-operating-characteristics curves were slightly different between some standards.

What are the clinical implications of this work?
A significant difference in relative risk for composite adverse perinatal outcome was found between the most- and least-stringent standards. Moreover, the INTERGROWTH-21st international and PRB/NICHD African-American customized standards are more suitable for fetal growth screening as compared with the Hadlock and Fetal Medicine Foundation standards in an African-American population.

ABSTRACT

Objective *To compare the predictive performance of estimated fetal weight (EFW) percentiles, according to eight growth standards, to detect fetuses at risk for adverse perinatal outcome.*

Methods *This was a retrospective cohort study of 3437 African-American women. Population-based (Hadlock, INTERGROWTH-21st, World Health Organization (WHO), Fetal Medicine Foundation (FMF)), ethnicity-specific (Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)), customized (Gestation-Related Optimal Weight (GROW)) and African-American customized (Perinatology Research Branch (PRB)/NICHD) growth standards were used to calculate EFW percentiles from the last available scan prior to delivery. Prediction performance indices and relative risk (RR) were calculated for EFW < 10th and > 90th percentiles, according to each standard, for individual and composite adverse perinatal outcomes. Sensitivity at a fixed (10%) false-positive rate (FPR) and partial (FPR < 10%) and full areas under the receiver-operating-characteristics curves (AUC) were compared between the standards.*

Results *Ten percent (341/3437) of neonates were classified as small-for-gestational age (SGA) at birth, and of these 16.4% (56/341) had at least one adverse perinatal outcome. SGA neonates had a 1.5-fold increased risk of any adverse perinatal outcome (P < 0.05). The screen-positive rate of EFW < 10th percentile varied from 6.8% (NICHD) to 24.4% (FMF). EFW < 10th percentile, according to all standards, was associated with an increased risk for each of the adverse perinatal*

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outcomes considered (P < 0.05 for all). The highest RRs associated with EFW < 10th percentile for each adverse outcome were 5.1 (95% CI, 2.1–12.3) for perinatal mortality (WHO); 5.0 (95% CI, 3.2–7.8) for perinatal hypoglycemia (NICHD); 3.4 (95% CI, 2.4–4.7) for mechanical ventilation (NICHD); 2.9 (95% CI, 1.8–4.6) for 5-min Apgar score < 7 (GROW); 2.7 (95% CI, 2.0–3.6) for neonatal intensive care unit (NICU) admission (NICHD); and 2.5 (95% CI, 1.9–3.1) for composite adverse perinatal outcome (NICHD). Although the RR CIs overlapped among all standards for each individual outcome, the RR of composite adverse perinatal outcome in pregnancies with EFW < 10th percentile was higher according to the NICHD (2.46; 95% CI, 1.9–3.1) than the FMF (1.47; 95% CI, 1.2–1.8) standard. The sensitivity for composite adverse perinatal outcome varied substantially between standards, ranging from 15% for NICHD to 32% for FMF, due mostly to differences in FPR; this variation subsided when the FPR was set to the same value (10%). Analysis of AUC revealed significantly better performance for the prediction of perinatal mortality by the PRB/NICHD standard (AUC = 0.70) compared with the Hadlock (AUC = 0.66) and FMF (AUC = 0.64) standards. Evaluation of partial AUC (FPR < 10%) demonstrated that the INTERGROWTH-21st standard performed better than the Hadlock standard for the prediction of NICU admission and mechanical ventilation (P < 0.05 for both). Although fetuses with EFW > 90th percentile were also at risk for any adverse perinatal outcome according to the INTERGROWTH-21st (RR = 1.4; 95% CI, 1.0–1.9) and Hadlock (RR = 1.7; 95% CI, 1.1–2.6) standards, many times fewer cases (2–5-fold lower sensitivity) were detected by using EFW > 90th percentile, rather than EFW < 10th percentile, in screening by these standards.

Conclusions *Fetuses with EFW < 10th percentile or EFW > 90th percentile were at increased risk of adverse perinatal outcomes according to all or some of the eight growth standards, respectively. The RR of a composite adverse perinatal outcome in pregnancies with EFW < 10th percentile was higher for the most-stringent (NICHD) compared with the least-stringent (FMF) standard. The results of the complementary analysis of AUC suggest slightly improved detection of adverse perinatal outcome by more recent population-based (INTERGROWTH-21st) and customized (PRB/NICHD) standards compared with the Hadlock and FMF standards. Published 2019. This article is a U.S. Government work and is in the public domain in the USA.*

INTRODUCTION

Low and high birth weight are associated with increased perinatal morbidity and mortality[1–17]. Therefore, antenatal surveillance of fetal growth is essential to ensure close monitoring and to suggest potential measures to reduce the risk (e.g. induction of labor)[18–27]. Indeed, antenatal detection of high-risk fetuses is associated with a significant reduction in stillbirth and perinatal morbidity rates[28–32].

Antenatal screening for growth restriction using ultrasound relies on estimation of fetal weight and comparison with a reference, also known as a growth chart or growth standard. The 10th and 90th percentile cut-offs, first suggested by Battaglia and Lubchenco[33] for birth weight and later adopted by Hadlock *et al.*[34] for estimated fetal weight (EFW), are used to identify fetuses at risk for adverse outcome[35–37].

After Hadlock's 'one-size-fits-all' growth chart was introduced, Gardosi *et al.*[38] proposed an adjustable fetal growth chart in which percentile curves are shifted up or down to account for non-pathologic factors such as maternal height, weight, parity, race/ethnicity and fetal sex[39–45]. The effects of these factors were assumed to be proportionally constant during gestation, and adjustment coefficients were estimated from birth weight data in specific populations[46–52]. More recent customized standards do not rely on the proportionality assumption and allow these effects to vary among the specific centile curves[53].

The potential of customized birth-weight standards to improve identification of neonates at risk for adverse perinatal morbidity and mortality is well established[54–67]. Nevertheless, recent initiatives to develop growth standards did not implement customization of growth charts, or they customized only for a subset of non-pathologic factors known to affect fetal growth. For example, the World Health Organization (WHO) growth standard customizes only by fetal sex[68–70], while the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) developed ethnicity-specific charts without adjusting for other factors[71]. In addition, the INTERGROWTH-21st project proposed a 'one-size-fits-all' standard without customization, yet the decision not to adjust for fetal sex was based on ethical grounds[72–76]. Similarly, the Fetal Medicine Foundation (FMF) proposed a non-customized fetal growth standard by reconciling fetal weight and birth weight data in a multi-ethnic population that included a large majority (69%) of white women[77].

Given the plethora of available fetal growth standards, with their intrinsic differences in design and in the characteristics of the populations from which they are derived, it is important to determine how these differences impact their utility. Therefore, we conducted a retrospective study comparing the ability of EFW < 10th and > 90th percentiles to identify fetuses at risk of perinatal morbidity and mortality according to eight growth standards.

METHODS

Study design

This was a retrospective cohort study conducted at the Center for Advanced Obstetrical Care and Research of the Perinatology Research Branch (PRB) (Detroit, MI, USA). All patients included in this study were enrolled in

research protocols approved by the Human Investigation Committee of Wayne State University and the Institutional Review Board of NICHD.

The study population consisted of pregnant women who had at least one ultrasound examination prior to delivery and for whom perinatal information was available. Women with a multiple gestation, those with known fetal anomaly or chromosomal aberration, and those who were lost to follow-up or delivered elsewhere were excluded from the study. Detailed demographic data, medical history and pregnancy outcomes were extracted from the patients' electronic medical records.

Outcomes

The adverse perinatal outcomes considered in this study were as follows: (1) perinatal mortality; (2) neonatal intensive care unit (NICU) admission; (3) Apgar score < 7 at 5 min after delivery; (4) neonatal hypoglycemia; (5) need for mechanical ventilation; (6) neonatal hypothermia; (7) meconium aspiration syndrome; and (8) composite adverse perinatal outcome, involving one or more of the outcomes above. Among these outcomes, only those affecting 20 or more of the 3437 patients were analyzed individually; otherwise, they contributed only to the analysis of composite adverse perinatal outcome.

Perinatal mortality was defined as stillbirth or neonatal death within 7 days after birth[78]. Stillbirth was defined as death of the fetus after 20 weeks of gestation, confirmed by ultrasound examination prior to delivery. NICU admission was defined as documented admission of the neonate to the NICU at any time during hospitalization. Apgar score at 5 min after delivery was calculated according to an accepted method for reporting the status of the neonate immediately after birth[79,80]. Neonatal hypoglycemia was defined as a glucose level < 45 mg/dL[81]. Mechanical ventilation was defined as when a ventilation machine was used to improve the exchange of air between the lungs and atmosphere. Neonatal hypothermia was defined as a neonatal axillary temperature $< 36.5°C$[78,82]. Meconium aspiration syndrome was diagnosed in infants who had dyspnea, tachycardia, need for supplemental oxygen within the first hours after delivery and diffuse irregular patchy infiltrates on chest radiographs[83]. Of note, infants with meconium below the vocal cords but with no clinical or radiographic evidence of disease were not diagnosed with aspiration syndrome.

Fetal growth screening

Screen positive for small- (SGA) and large- (LGA) for-gestational age was based on EFW $< 10^{th}$ and EFW $> 90^{th}$ percentile, respectively, for each standard. The observed EFW at the last scan prior to delivery was derived using the formula published for each individual standard based on biometric parameters (abdominal circumference (AC), femur length (FL), head circumference (HC) and biparietal diameter (BPD)).

For Hadlock 1, EFW was calculated by a three-parameter equation (HC, AC and FL), developed by Hadlock *et al.*[84] and applied in other recent growth standards (NICHD, WHO, PRB/NICHD, FMF), and was compared with the same centile curves reported by Hadlock *et al.* in 1991[34] using a four-parameter equation (AC, FL, HC and BPD).

For Hadlock 2, EFW was calculated by the four-parameter formula (AC, FL, HC and BPD), originally reported by Hadlock *et al.*[84], and the observed value was compared with the centile curves derived for this EFW formula[34]. This fetal weight assessment method was utilized clinically to detect SGA in the study population.

For the PRB/NICHD standard, EFW was calculated using the three-parameter Hadlock formula (HC, AC and FL)[84] and corresponding customized centiles were calculated using the R package available at http://bioinformaticsprb.med.wayne.edu/software/prb-nichd-fetal-growth-standard/. Growth centiles were customized for maternal height, weight and parity, and fetal sex[53].

For the NICHD standard, EFW was calculated using the three-parameter Hadlock formula (HC, AC and FL)[84] and compared with the centile curves derived for the African-American population[71].

For the Gestation-Related Optimal Weight (GROW) standard, EFW was calculated using the three-parameter Hadlock formula (HC, AC and FL)[84] and a corresponding customized percentile was obtained using GROW software (V8.0.1)[85]. Percentiles were customized for maternal ethnic origin, height, weight and parity, and fetal sex.

For the WHO fetal growth standard, EFW was calculated based on the three-parameter Hadlock formula (HC, AC and FL)[84] and was compared with the reference charts without customization for fetal sex[68–70].

For the INTERGROWTH-21st standard, EFW was calculated from AC and HC using the equation proposed by the authors, and observed values were compared with the reported centile curves[75,86].

For the FMF standard, EFW was calculated based on the three-parameter Hadlock formula (HC, AC and FL)[84] and compared with the reference charts developed by Nicolaides *et al.*[77].

Classification of neonates as SGA (birth weight $< 10^{th}$ percentile) or LGA (birth weight $> 90^{th}$ percentile) at birth was in accord with the USA national reference for birth-weight standards reported by Alexander *et al.*[87].

Statistical analysis

Sensitivity and specificity of the screening test and the relative risk (RR) associated with EFW $< 10^{th}$ and $> 90^{th}$ percentiles were evaluated for each standard for each outcome. When screening for SGA by the standards that provide an exact percentile for any given observed EFW value (GROW, Hadlock, INTERGROWTH-21st, PRB/NICHD, FMF), receiver-operating-characteristics (ROC) curves were constructed and the full and partial (false-positive rate (FPR) $< 10\%$) areas under the ROC

curves (AUC) were calculated and compared with those of Hadlock 1, using the pROC package[88]. We chose to calculate partial AUCs to assess which standards have a higher sensitivity at a low and, hence, more clinically relevant FPR. For these standards, sensitivity at a 10% FPR was also determined for each outcome in screening by EFW $< 10^{th}$ percentile to evaluate the extent to which differences in sensitivity are due to different overall stringencies of the standards.

RESULTS

Study population

The study population included 3437 African-American women, the characteristics of whom are summarized in Table 1. Of these women, 478 (13.9%) delivered preterm (< 37 weeks of gestation) and 2959 (86.1%) delivered at term. The median gestational age at delivery was 39.0 (interquartile range (IQR), 38.0–39.9) weeks, and the median interval from sonographic EFW measurement to delivery was 2.6 (IQR, 1.0–5.3) weeks. Median maternal body mass index of the population was 27.5 (IQR, 22.9–33.7) kg/m^2, and 18.4% (634/3437) of women were smokers. At delivery, 9.9% (341/3437) of neonates were classified as SGA and 7.3% (250/3437) as LGA. In the cohort, 11.7% (403/3437) of neonates were diagnosed with at least one adverse perinatal outcome, 219 of whom were delivered preterm. The 20 cases of perinatal mortality included 11 stillbirths and nine neonatal deaths.

Of the neonates with at least one adverse perinatal outcome, 13.9% (56/403) were SGA (birth weight $< 10^{th}$ centile). A forest plot of the RR of adverse perinatal outcomes in pregnancies with birth weight $< 10^{th}$ centile is shown in Figure S1. The RR for composite adverse perinatal outcome associated with SGA at delivery was 1.5 (95% CI, 1.15–1.94), and the highest RR for the individual outcomes was for neonatal hypoglycemia (3.49; 95% CI, 2.23–5.46).

Table 1 Characteristics of study population of 3437 singleton pregnancies

Characteristic	*Statistic*
Maternal age (years)	23 (20–27)
Parity	
Nulliparous	1259 (36.6)
Parous	2178 (63.4)
Body mass index (kg/m^2)	27.5 (22.9–33.7)
Maternal height (cm)	162.6 (157.5–167.6)
Maternal weight (kg)	72.6 (60.8–90.3)
Smoking status	
Smoker	634 (18.4)
Non-smoker	2803 (81.6)
Gestational age at delivery (weeks)	39.0 (38.0–39.9)
Interval from scan to delivery (weeks)	2.6 (1.0–5.3)
Preterm delivery	478 (13.9)
Mode of delivery	
Vaginal	2475 (72.0)
Cesarean section	962 (28.0)
Fetal sex	
Male	1755 (51.1)
Female	1682 (48.9)
Birth weight (g)	3145 (2790–3465)
Small-for-gestational age	341 (9.9)

Data are given as median (interquartile range) or *n* (%). Maternal height and weight were recorded in inches and pounds and then converted into cm and kg, respectively, prior to analysis.

Association between estimated fetal weight < 10th percentile and adverse perinatal outcome

Screen-positive rates

There was large variability in the screen-positive rate of EFW $< 10^{th}$ percentile across the different standards: 6.8% for NICHD, 9.4% for GROW, 11.6% for WHO, 13.2% for INTERGROWTH-21st, 13.5% for PRB/NICHD, 16.2% for Hadlock 2, 16.5% for Hadlock 1 and 24.4% for FMF.

Relative risk

EFW $< 10^{th}$ percentile at the last scan before delivery was associated with an increased risk in individual and composite adverse perinatal outcomes for all standards (Figure 1, Tables 2 and S1). The RR for composite adverse perinatal outcome was significantly lower according to the least-stringent (FMF) (RR = 1.47; 95% CI, 1.2–1.8) compared with the most-stringent (NICHD) (RR = 2.46; 95% CI, 1.9–3.1) standard. The highest RRs for each individual adverse outcome were: 5.05 (95% CI, 2.08–12.29) for perinatal mortality (WHO); 5.0 (95% CI, 3.20–7.83) for neonatal hypoglycemia (NICHD); 3.39 (95% CI, 2.43–4.74) for mechanical ventilation (NICHD); 2.88 (95% CI, 1.80–4.63) for Apgar score < 7 at 5 min (GROW); and 2.68 (95% CI, 2.01–3.57) for NICU admission (NICHD). Of note, for all individual outcomes, the CIs of the RR overlapped between standards. Nonetheless, there were notable differences in RR estimates between standards for specific outcomes. For example, in perinatal mortality, the lowest RR was 2.18 (Hadlock 1) and the highest was 5.05 (WHO).

Sensitivity and specificity

The sensitivity of EFW $< 10^{th}$ centile for composite adverse perinatal outcome ranged between 15% (NICHD) and 32% (FMF), with these two standards having the highest (27%) and lowest (16%) positive predictive values, respectively (Table S1). The highest sensitivities for each individual outcome at the 10th percentile cut-off were obtained using the FMF standard: 46% for neonatal hypoglycemia; 45% for perinatal mortality; 40% for mechanical ventilation; 35% for NICU admission; and 35% for 5-min Apgar score < 7. The higher sensitivities of the FMF standard were typically accompanied by lower specificities. The specificity for composite adverse perinatal outcome ranged between 77% (FMF) and 94% (NICHD). The highest specificities for individual outcomes were all achieved using the NICHD standard and were as follows:

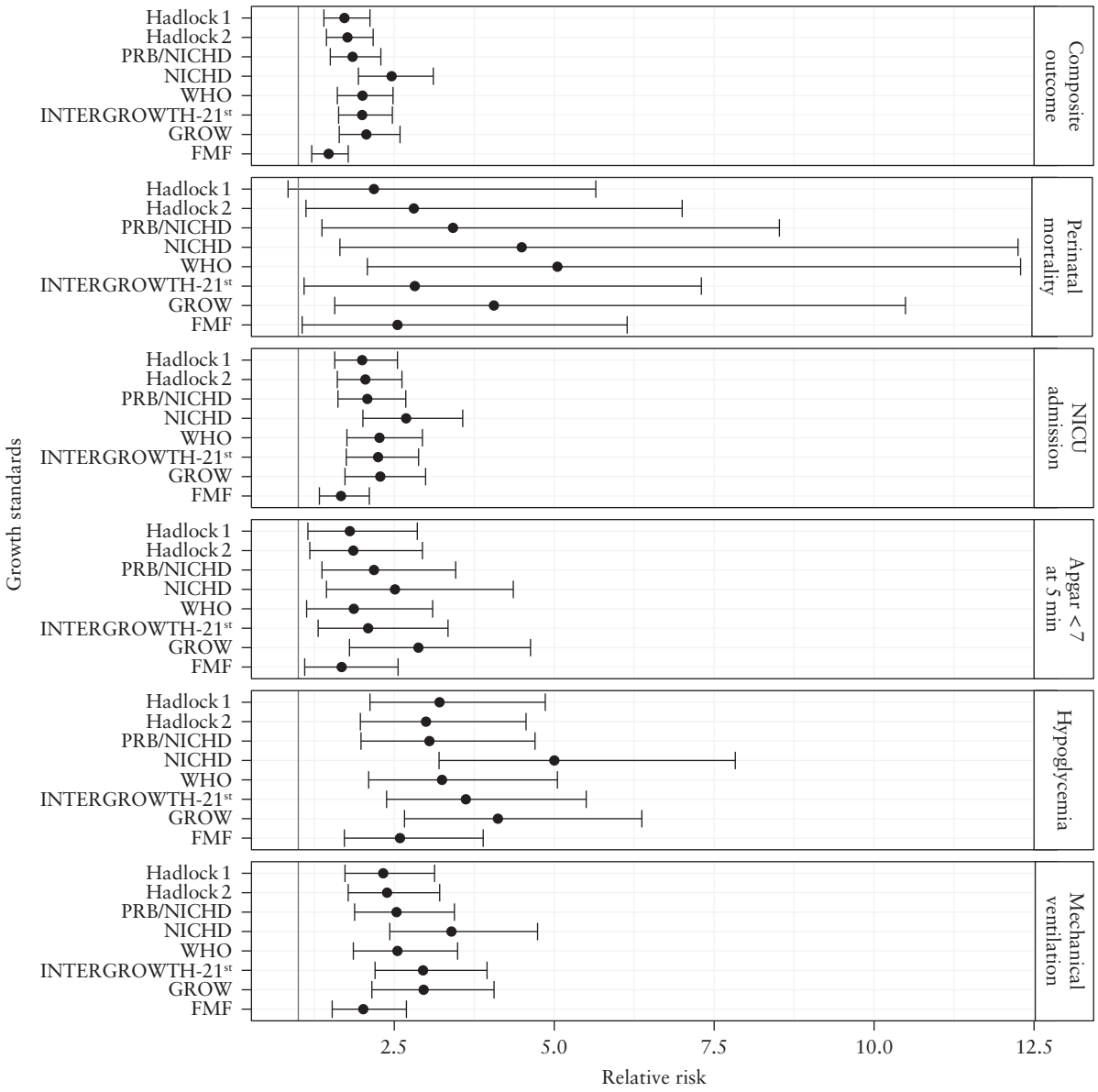

Figure 1 Forest plots showing relative risk of adverse perinatal outcome in pregnancies with estimated fetal weight < 10th centile, according to fetal growth standard. FMF, Fetal Medicine Foundation; GROW, Gestation-Related Optimal Weight; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; PRB/NICHD, Perinatology Research Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; WHO, World Health Organization.

94% for neonatal hypoglycemia; 93% for perinatal mortality; 94% for mechanical ventilation; 94% for NICU admission; and 93% for 5-min Apgar score < 7 (Table S1).

Sensitivity at fixed false-positive rate

To determine the degree to which the differences in sensitivities between standards are due to different levels of stringency (hence, specificity), sensitivity at a fixed (10%) FPR was determined for the standards providing an exact percentile value. This analysis revealed a high degree of similarity in sensitivity of the standards (Figure 2). For instance, sensitivity (at 10% FPR) for composite adverse outcome varied only from 19.4% (GROW) to 21.7% (INTERGROWTH-21st) among the six standards, while, for perinatal mortality, it was the same (30%) for all. For the FPR for composite adverse outcome to be the same (10%) among the standards, an EFW percentile cut-off of 6.6 was required for Hadlock 1, 8.0 for both PRB/NICHD and INTERGROWTH-21st, 11.2 for GROW, and 2.0 for FMF.

Receiver-operating-characteristics-curve analysis

The AUCs for low EFW percentiles in the prediction of individual and composite outcomes demonstrated either very poor (AUC, 0.5–0.6) or poor (AUC, 0.6–0.7) performance, with generally similar values among the different growth standards (Figure 3 and Tables 3 and S3). However, the PRB/NICHD standard had a higher AUC (0.70) for the prediction of perinatal mortality compared with the Hadlock 1 (0.66) and FMF (0.64) standards

Table 2 Relative risk of adverse perinatal outcome in pregnancies with estimated fetal weight < 10th percentile, according to fetal growth standard

			Fetal growth standard							
Outcome	n	PTD < 37 weeks (n)	*Hadlock 1*	*Hadlock 2*	*PRB/NICHD*	*NICHD*	*WHO*	*INTERGROWTH-21st*	*GROW*	*FMF*
Composite adverse perinatal outcome	403	219	1.72 (1.40–2.12)	1.77 (1.44–2.17)	1.85 (1.50–2.29)	2.46 (1.94–3.11)	2.00 (1.61–2.48)	2.00 (1.63–2.47)	2.06 (1.64–2.59)	1.47 (1.21–1.78)
Perinatal mortality	20	17	2.18 (0.84–5.65)	2.81 (1.12–7.00)	3.42 (1.37–8.52)	4.49 (1.65–12.25)	5.05 (2.08–12.29)	2.82 (1.09–7.30)	4.06 (1.57–10.49)	2.55 (1.06–6.14)
NICU admission	282	176	2.00 (1.57–2.55)	2.05 (1.61–2.62)	2.08 (1.62–2.68)	2.68 (2.01–3.57)	2.27 (1.76–2.94)	2.25 (1.75–2.88)	2.28 (1.73–2.99)	1.67 (1.33–2.11)
Apgar < 7 at 5 min	91	48	1.81 (1.15–2.86)	1.86 (1.18–2.94)	2.18 (1.37–3.46)	2.51 (1.44–4.36)	1.87 (1.13–3.10)	2.09 (1.31–3.34)	2.88 (1.80–4.63)	1.68 (1.10–2.56)
Hypoglycemia	90	58	3.21 (2.12–4.86)	3.00 (1.97–4.56)	3.05 (1.98–4.70)	5.00 (3.20–7.83)	3.25 (2.10–5.05)	3.62 (2.38–5.50)	4.12 (2.66–6.37)	4.56 (2.95–7.05)
Mechanical ventilation	187	148	2.33 (1.73–3.13)	2.39 (1.78–3.21)	2.54 (1.88–3.44)	3.39 (2.43–4.74)	2.55 (1.86–3.49)	2.95 (2.20–3.95)	2.96 (2.15–4.06)	2.02 (1.53–2.69)

Values in parentheses are 95% CI. FMF, Fetal Medicine Foundation; GROW, Gestation-Related Optimal Weight; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; PRB/NICHD, Perinatology Research Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; PTD, preterm delivery; WHO, World Health Organization.

($P < 0.05$ for both). The AUC was also slightly higher for the Hadlock 2 standard (AUC = 0.67) compared with the FMF standard (AUC = 0.64) for perinatal mortality (Table S3), and for the INTERGROWTH-21st standard (AUC = 0.58) compared with the FMF standard (AUC = 0.56) for 5-min Apgar < 7 ($P < 0.05$ for both).

Nevertheless, when considering only the part of the ROC curve for which the FPR was < 10% in the calculation of AUC (partial AUC), the INTERGROWTH-21st standard had slightly better performance compared with the Hadlock 1 and FMF standards for the prediction of NICU admission ($P < 0.05$ for both) (Figure 3, Tables 3 and S3). Similarly, the partial AUC was slightly higher for the INTERGROWTH-21st compared with the FMF standard for hypoglycemia ($P < 0.01$) (Figure 3, Table S3).

Association between estimated fetal weight > 90th percentile and adverse perinatal outcome

The screen-positive rates of EFW > 90th percentile were overall lower than those of EFW < 10th percentile but similarly varied greatly between the standards: 2.8% for Hadlock 2, 2.9% for Hadlock 1, 6.4% for GROW, 7.0% for INTERGROWTH-21st, 8.8% for PRB/NICHD, 9.6% for FMF, 10.2% for WHO and 12.5% for NICHD. Among the eight standards considered, EFW > 90th percentile according to the INTERGROWTH-21st (RR = 1.4; 95% CI, 1.0–1.9) and Hadlock 2 (RR = 1.7; 95% CI, 1.1–2.6) standards was associated significantly with composite adverse perinatal outcome, yet sensitivity was 2- to 5-fold lower (5% for Hadlock and 10% for INTERGROWTH-21st) compared with that for EFW < 10th percentile according to these standards (Table S2). LGA fetuses were also at risk of hypoglycemia according to the Hadlock 2 standard (RR = 2.9; 95% CI, 1.4–6.1), with only 8% (sensitivity) of cases being detected.

DISCUSSION

Customized *vs* non-customized standards

More than 100 fetal growth standards have been proposed for fetal growth assessment[41]. Several studies suggested that customized fetal growth[38,45,89,90] and birth weight[54–67] assessment better predicts morbidity, while other studies found the opposite or were inconclusive[39,40,55,57,66,91–105]. Sovio and Smith[66] reported that customized third-trimester growth assessment did not improve the association with neonatal morbidity compared with non-customized standards, while Blue *et al.*[103] reported superior performance of non-customized standards than of ethnicity-specific standards. We therefore compared eight fetal growth standards for the prediction of adverse perinatal outcomes and evaluated the extent to which differences in sensitivity result from different overall stringencies of the standards (i.e. how low the 10th centile curve and, hence, the screen-positive rate are) as opposed to differences in the shape of the 10th percentile curve and/or factors

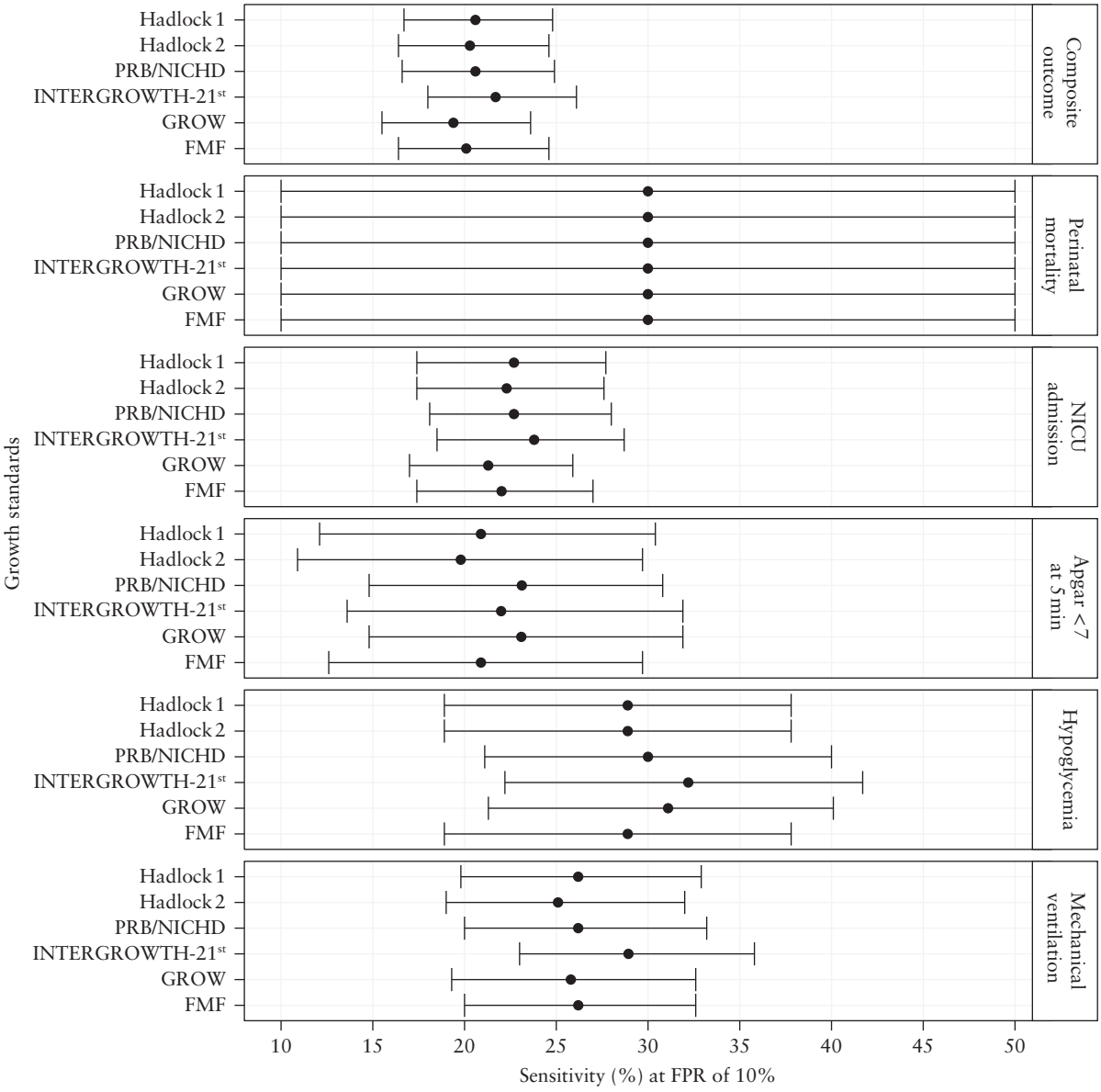

Figure 2 Forest plots showing sensitivity, at fixed (10%) false-positive rate (FPR), of low estimated fetal weight percentile for adverse perinatal outcome, according to fetal growth standard. Only standards providing an exact percentile value are included. Test positive is based on cut-off chosen so that FPR is 10% for each outcome considered. FMF, Fetal Medicine Foundation; GROW, Gestation-Related Optimal Weight; NICU, neonatal intensive care unit; PRB/NICHD, Perinatology Research Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

considered in the customization that lead to different percentiles across standards for the same observed EFW.

Comparison of screen-positive rates

The screen-positive rate for SGA and LGA varied considerably, with the NICHD African-American standard identifying only 6.8% of fetuses as SGA and 12.5% as LGA; hence, this standard can be considered overall too low for our population. By contrast, Hadlock's chart identified 16.5% of fetuses as SGA and only 2.9% as LGA; hence, this standard can be considered too high. Although the 10th percentile of EFW according to the FMF standard was the highest compared with all standards, resulting in the largest screen-positive rate for SGA (24.4%), the 90th centile of this chart was similar to that of the other standards and classified 9.6% of fetuses as LGA, based on the last available scan.

While a previous study[65] in a USA population identified a large difference in the screen-positive rate of birth weight $< 10^{th}$ percentile between the INTERGROWTH-21st (3.5%) and GROW (11.1%) standards, the assessment of EFW presented herein resulted in less discrepancy (9.4%, GROW; 13.2%, INTERGROWTH-21st), which is likely due to differences in the populations.

Comparison of relative risks

Sovio *et al.*[23] reported that a third-trimester EFW $< 10^{th}$ percentile was associated with a 1.6-fold increase in

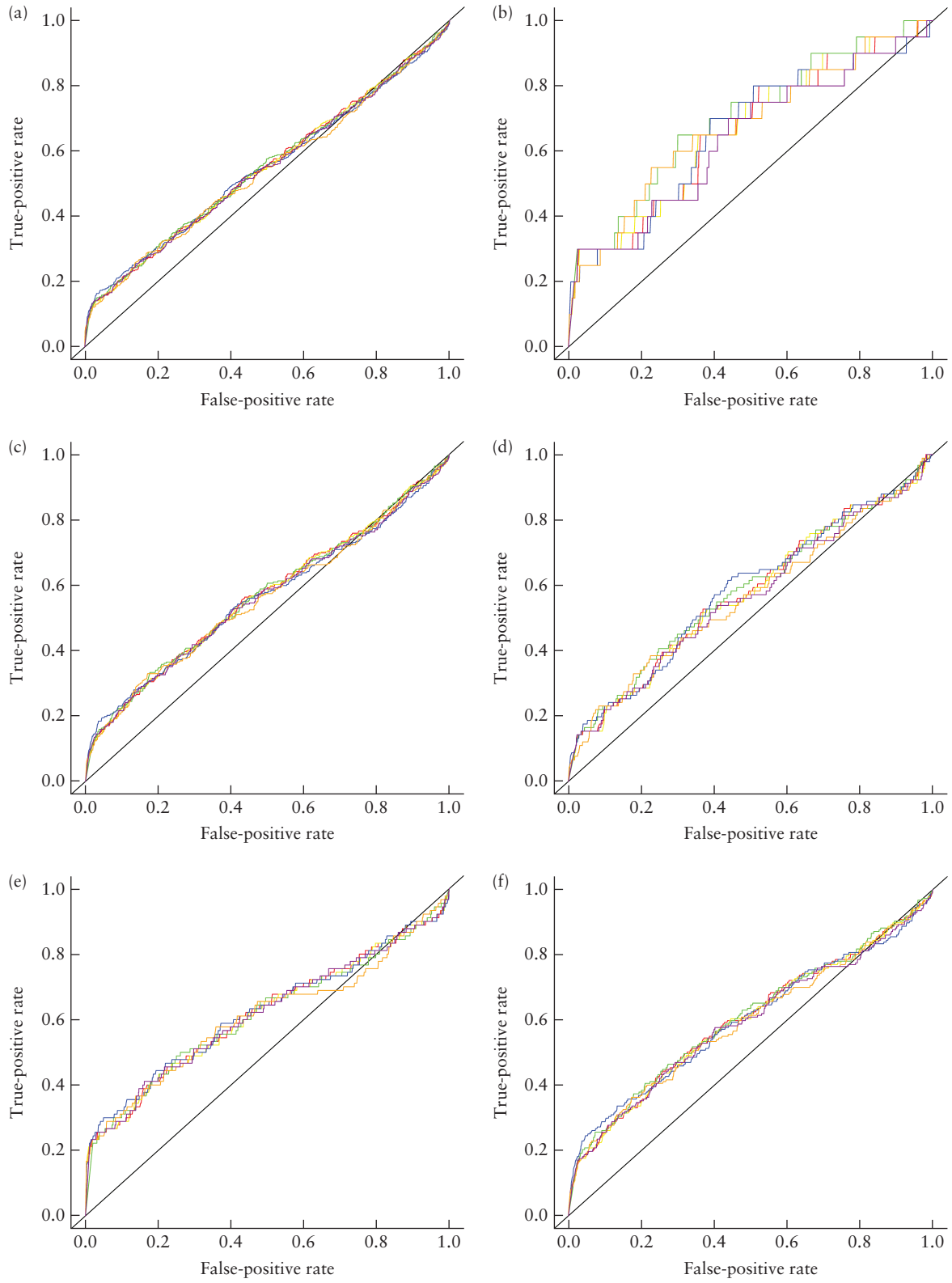

Figure 3 Receiver-operating-characteristics (ROC) curves for low estimated fetal weight percentile in prediction of composite adverse perinatal outcome (a), perinatal mortality (b), neonatal intensive care unit (NICU) admission (c), 5-min Apgar score < 7 (d), hypoglycemia (e) and mechanical ventilation (f), using Hadlock 1 (——), Hadlock 2 (——), Perinatology Research Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (PRB/NICHD) (——), INTERGROWTH-21st (——), Gestation-Related Optimal Weight (GROW) (——) and Fetal Medicine Foundation (FMF) (——) growth standards. ROC curves are constructed from percentile values derived from each standard.

Table 3 Area under the receiver-operating-characteristics curve (AUC) for prediction of adverse perinatal outcome by low estimated fetal weight percentile, according to fetal growth standard

	AUC		*Partial AUC (FPR < 10%)*	
Outcome/standard	*Value*	P	*Value*	P
Composite adverse perinatal outcome				
Hadlock 1	0.549	Ref	0.015	Ref
Hadlock 2	0.547	0.082	0.015	0.517
PRB/NICHD	0.550	0.781	0.015	0.541
INTERGROWTH-21st	0.547	0.675	0.016	0.036
GROW	0.541	0.107	0.014	0.405
FMF	0.544	< 0.001	0.015	0.313
Perinatal mortality				
Hadlock 1	0.662	Ref	0.026	Ref
Hadlock 2	0.668	0.157	0.026	0.406
PRB/NICHD	0.699*	0.011	0.026	0.803
INTERGROWTH-21st	0.657	0.827	0.024	0.495
GROW	0.675	0.554	0.023	0.256
FMF	0.640	0.001	0.026	0.991
NICU admission				
Hadlock 1	0.568	Ref	0.015	Ref
Hadlock 2	0.566	0.200	0.015	0.627
PRB/NICHD	0.569	0.856	0.016	0.520
INTERGROWTH-21st	0.562	0.285	0.017†	0.017
GROW	0.559	0.148	0.015	0.576
FMF	0.562	< 0.001	0.015	0.440
5-min Apgar score < 7				
Hadlock 1	0.574	Ref	0.014	
Hadlock 2	0.572	0.263	0.013	0.105
PRB/NICHD	0.581	0.287	0.015	0.101
INTERGROWTH-21st	0.584	0.272	0.016	0.179
GROW	0.563	0.246	0.014	0.708
FMF	0.563	0.001	0.014	0.827
Hypoglycemia				
Hadlock 1	0.617	Ref	0.025	Ref
Hadlock 2	0.614	0.151	0.025	0.828
PRB/NICHD	0.614	0.557	0.023	0.198
INTERGROWTH-21st	0.622	0.656	0.027	0.072
GROW	0.608	0.423	0.025	0.546
FMF	0.615	0.425	0.024	0.362
Mechanical ventilation				
Hadlock 1	0.600	Ref	0.018	Ref
Hadlock 2	0.596	0.039	0.018	0.558
PRB/NICHD	0.606	0.194	0.019	0.064
INTERGROWTH-21st	0.598	0.843	0.022†	0.003
GROW	0.591	0.295	0.018	0.656
FMF	0.591	< 0.001	0.018	0.550

*AUC significantly higher by ≥ 2%, †partial AUC significantly higher by ≥ 0.2%, compared with Hadlock 1. FMF, Fetal Medicine Foundation; FPR, false-positive rate; GROW, Gestation-Related Optimal Weight; NICU, neonatal intensive care unit; PRB/NICHD, Perinatology Research Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; Ref, reference.

the risk of neonatal morbidity, which is similar to the RR estimate of 1.7 derived for Hadlock's standard in the current study. Moreover, we showed that fetuses with EFW $< 10^{th}$ percentile were at increased risk of individual adverse perinatal outcomes according to all standards, with the highest risk estimate being for perinatal mortality (WHO, RR = 5.05). Overall, the most-stringent standard for SGA screening (NICHD) resulted in consistently higher relative risk estimates for adverse perinatal outcomes, while the least-stringent standard (FMF) had the lowest relative risk estimates. The differences in relative risk between these standards were significant for composite adverse perinatal outcome, yet the overlapping confidence intervals between all other standards impeded drawing conclusions regarding the superiority of one standard over another for individual adverse perinatal outcomes.

Comparison of area under ROC curve

To complement the typical analysis based on relative risk and sensitivity for adverse perinatal outcomes[65], we also compared the full and partial AUCs of low EFW percentiles. While sensitivity may vary due to differences in screen-positive rate, AUC analysis considers all possible cut-offs and compares standards in terms of their ability

to rank fetuses from the most (lowest percentile) to the least (highest percentile) at risk of suboptimal growth. Even for non-customized standards, such differences in the reordering of fetuses with respect to their risk are expected, given the shape of the 10th-percentile curve, which, for the same screen-positive rate, alters the balance of preterm and term fetuses diagnosed as screen positive in a given cohort. Performance differences among growth standards are also expected given the differences in the pregnancy characteristics considered in customization (if any) and analytical approaches and in populations used to establish the standards[106].

The AUC for prediction of perinatal mortality using the PRB/NICHD standard was higher than that for the Hadlock 1 and FMF standards, yet the improvement emerged at FPR > 15%; hence, a difference was not detected when comparing the partial AUCs (FPR < 10%). Of note, the 20th percentile cut-off according to the PRB/NICHD growth standard identifies one-half of fetuses at risk of perinatal mortality and one-third of those at risk of any of the adverse perinatal outcomes considered (Figure 3).

Based on partial AUC, the INTERGROWTH-21st standard showed superiority over the Hadlock and FMF standards for individual perinatal outcomes. This was expected as fetuses at risk for these outcomes had lower EFW percentiles according to INTERGROWTH-21st compared with the Hadlock and FMF standards, resulting in higher sensitivity at a low FPR (Figure 3, Tables 3 and S3). Therefore, the ROC curve-based analyses provided a perspective not attainable by simply comparing relative risk at the 10% EFW cut-off.

Strengths and limitations

This is the first study to compare eight fetal growth standards used worldwide, for the prediction of adverse perinatal outcomes in a single population. The limitations of this study are that: (1) the population comprised only African-American women and that future studies are therefore required to determine whether these findings extrapolate to other populations; (2) the population included a wide range of gestational ages at the last ultrasound scan prior to delivery, which was related to the actual distribution of gestational age at delivery; (3) several but not all adverse perinatal outcomes were evaluated, due to their low frequencies; (4) the cohort included in this study was derived from a larger set of 4001 pregnancies used to develop the PRB/NICHD standard; hence, prediction performance estimates for this particular standard may be biased.

Conclusions

This study demonstrates that differences in stringency (and hence FPR) between fetal growth standards explain the variability in sensitivity and relative risk for adverse perinatal outcomes. When considering a wider range of FPR using ROC curve analysis, the recent international (INTERGROWTH-21st) and customized (PRB/NICHD) standards seem to improve detection of fetuses at risk of some adverse perinatal outcomes in an African-American population, compared with Hadlock and FMF standards. Although LGA fetuses were also at risk of adverse perinatal outcomes, many fewer cases are detected by LGA than SGA screening.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Forest plot showing relative risk of adverse perinatal outcomes in pregnancies with small-for-gestational-age neonate (birth weight < 10th centile). NICU, neonatal intensive care unit.

Table S1 Association between an EFW < 10th percentile and adverse perinatal outcomes, according to fetal growth standard

Table S2 Association between an EFW > 90th percentile and adverse perinatal outcomes, according to fetal growth standard

Table S3 Area under ROC curves for prediction of adverse perinatal outcomes by low EFW percentile, according to fetal growth standard, using the Fetal Medicine Foundation standard as reference

